Remarks

Reconsideration of this Application is respectfully requested.

Upon entry of the foregoing amendment, claims 1-71 are pending in the application, with claims 1, 43, 47, 55, 61, 66 and 68 being the independent claims. Claims 4, 12, 23-26, 50, 57, 63, 66 and 67 are sought to be canceled without prejudice to or disclaimer of the subject matter therein. Claims 21, 22, 43, 44 and 68 are amended merely to remove non-elected subject matter from the claims. Claims 54 and 65 are amended to disclaim one or more members of a Markush group. Claims 47, 55 and 61 are amended to remove non-elected subject matter and to disclaim one or more members of a Markush group. New claims 69-71 have been added. These changes are believed to introduce no new matter, and their entry is respectfully requested.

Based on the above amendment and the following remarks, Applicants respectfully request that the Examiner reconsider all outstanding objections and rejections and that they be withdrawn.

The Restriction Requirement

Applicants affirm the provisional election made by telephone on June 20, 2005 to prosecute the invention of Group I, claims 1-3, 5-11, 13-22, 27-49, 51-56, 58-62, 64, 65 and 68. Claims 4, 12, 23-26, 50, 57, 63, 66 and 67 are withdrawn from consideration.

Rejections under 35 U.S.C. § 112

Claims 1-3, 5-11, 13-22, 27-42, 45 and 46 have been rejected under 35 U.S.C. §112, first paragraph, allegedly because the specification does not enable treating or

ameliorating any cancer or disorder responsive to the induction of apoptosis or treating breast cancer using all possible prodrugs of compounds of formula I or using a combination of instant compounds of formula I with other drugs. (office action pages 3-4). The Examiner states:

> At present, the caspase family of cysteine proteases comprises 14 different members, and more may be discovered in the future. The Applicants provide some data on Caspase activity in Table 1 on page 74 and also show inhibitory effect on cell proliferation using breast cancer cell lines (see table II). In regard to Caspase activity, first of all, it is not clear from the data which member of already known 14 different members of Caspase family of cysteine proteases was used in this study. Secondly, there is a lot of unpredictability even using this one member since there is huge variation in EC50 values among 13 compounds tested (see data in table I). There is no teaching either in the specification or prior art showing involvement of this specific cysteine protease in induction of apoptosis in every known cancer or disorder in the art. There is no working examples present showing efficacy of instant compounds alone, their prodrugs, or combination of instant compounds with any other drug in known animal models of every known disorder responsive to apoptosis or all known cancer lines. There is no direction or guidance present in the specification how the instant compounds having activating effect on only one member of Caspase family or having inhibitory effect on cell proliferation using only breast cancer cell line in vitro will be able to treat and/or ameliorate every possible known disorder responsive to induction of apoptosis by all 14 different members of cysteine proteases.

Office action, pages 4-5 (emphasis in the original). Applicants respectfully traverse this rejection.

The test for enablement is whether one reasonably skilled in the art could make or use the invention from the disclosures in the application coupled with information known in the art without undue experimentation. The compounds of the present claims are enabled for inducing cell death if the class of compounds as a whole is capable of inducing apoptosis, without knowing which of the caspase family member is involved.

Prior to Applicant's effective filing date, it was known that cancer cells are, *inter alia*, generally characterized not only by a loss of cell cycle control but also by resistance to apoptosis. *See generally* Raymond W. Ruddon, *Biochemistry of Cancer, in* Holand-Frei Cancer Medicine, Chapter 7 (Robert C. Blast, Jr., *et al.* eds., 5th ed., B.C. Decker, 2000), a copy of which is submitted herewith as Exhibit B. Consequently, increasing the rate of apoptosis is recognized by those of skill in the art as an effective method of treating a wide variety of cancers. *See, e.g.*, WO 00/04901, page 3, line 3, through page 5, line 6, a copy of which is submitted herewith as Exhibit C. Indeed, caspase activation is recognized, by those of skill in the art of cancer therapy, as a crucial requirement for the sensitivity of tumor cells toward drug-induced cell death. *See, e.g.,* Los, M. *et al., Blood 90*:3118-3129, 3128 (1997), a copy of which is enclosed herewith as Exhibit D. Moreover, all caspases known to be present in adult tissues play some role in apoptosis. For example, the web page of the Department of Biochemistry and Immunology at St George's, University of London, lists apoptosis as one of the functions of thirteen of fourteen known caspases (caspase-1 to caspase-13). *See* http://www.sgul.ac.uk/depts/immunology/~dash/apoptosis/caspases.html, last accessed September 14, 2005, a copy of which is enclosed herewith as Exhibit E. However, caspase-14 is highly expressed in embryonic tissues but is apparently absent from adult tissues. *See* Hu, S. et al. *J. Biol. Chem.* 273:29648-653 (1998), a copy of which is enclosed herewith as Exhibit F. Thus, all the caspases known to be present in adult tissues appear to play a role in apoptosis. Therefore, it is now recognized by those of skill in the art that agents that increase the rate of apoptosis are effective for the treatment of a wide variety of cancers.

Moreover, the Examiner asserts that "there is no teaching either in the specification or prior art showing involvement of this cysteine protease in induction of apoptosis in every known cancer or disorder in the art." Office Action page 5. However, as pointed out above, 13 of 14 known caspases are present in adult tissue cells and each one of the 13 caspases, when activated, is capable of inducing apoptosis. Accordingly, the compounds claimed in the present invention should induce apoptosis in all adult cells.

The Examiner also alleges that "there is no working examples present showing efficacy of instant compounds alone, their prodrugs, or a combination of instant compounds with any other drug in known animal models of every known disorder responsive to apoptosis or all known cancer cells." Applicants point out that the specification provides working examples which illustrate the ability of the claimed compounds to induce apoptosis. See Example 84 and Table I where the apoptotic activities of 14 compounds are demonstrated. Moreover, the enablement of the present claims does not require the existence of such a "magic bullet." In order for the present claims to be enabled for the treatment of cancer, it is sufficient that the class of compounds as a whole has caspase activating activity and that administration of compounds having such activity is capable of treating cancers in general. To the extent that any particular compound within the genus is not effective or is less effective than other compounds within the genus, it is merely an inoperative or less effective embodiment of the claimed invention. As long as the skilled artisan can readily determine which embodiments are inoperative without undue experimentation, the invention as a whole is enabled. See M.P.E.P. 2164.08(b). The examples disclosed in

the present specification involving one type of cancer cells and fourteen different compounds of the claimed invention indicate that the compounds are effective in inducing apoptosis in cancer cells. Additional examples are provided in a 37 C.F.R. § 1.132 declaration by the co-inventor Dr. Sui Xiong Cai submitted herewith as Exhibit A. The examples disclosed in the present specification and in the declaration involve two types of human breast cancer cell lines, two types of human colon cancer cell lines, a human lung cancer cell line, a human prostate cancer cell line and a murine pre-B cell lymphoma cell line as well as 29 different compounds of the claimed invention. These examples provide further evidence that the claimed compounds are generally effective in inducing apoptosis in cancer cells.

The Examiner further alleges that the specification does not enable using a combination of the compounds of formula I with other drugs. (office action pages 3-4).

The specification (page 25, lines 9-17) discloses that "the compound of the invention may be administered together with the at least one known chemotherapeutic agent as part of a unitary pharmaceutical composition." Claim 45 requires that the pharmaceutical composition comprising the compounds of formula I additionally comprises at least one known cancer chemotherapeutic agent and claim 46 specifies the chemotherapeutic agent. The experimentation required to add a known cancer chemotherapeutic agent to the pharmaceutical composition of the compounds of formula I cannot be undue. Applicants respectfully request that the rejection be withdrawn.

Therefore, Applicants respectfully request that the rejection of claims 1-3, 5-11, 13-22, 27-42, 45 and 46 based on 35 U.S.C. §112, first paragraph, be withdrawn.

The Examiner rejected claims 1-3, 5-11, 13-22, 27-49, 51-56, 58-62, 64, 65 and 68 under 35 U.S.C. §112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which the applicant regards as the invention. The Examiner alleges that the term "prodrug" in claims 1-3, 5-11, 13-22, 27-49, 51-56, 58-62, 64, 65 and 68 is indefinite because specific prodrugs and methods of preparing them are not defined. The Examiner further alleges that the term "ameliorating" is indefinite because the degree or amelioration is not defined and it is not clear how this amelioration is assessed in vivo following administration of compounds of formula I. Office Action page 6. Applicants respectfully traverse this rejection.

To expedite the prosecution of the pending claims, Applicants have amended claims 1, 27 and 30 by deleting the terms "ameliorating" and "amelioration" and by limiting the term "prodrug" to specifically described types of prodrugs. Support for this amendment is found in the specification page 20, lines 1-11. Reconsideration and withdrawal of the rejection of claims 1-3, 5-11, 13-22, 27-49, 51-56, 58-62, 64, 65 and 68 under 35 U.S.C. § 112, second paragraph, based on the indefiniteness of the terms "ameliorating" and "prodrug" is respectfully requested.

Rejections under 35 U.S.C. § 102

Claims 47-49, 52-56, 59-62 and 65 are rejected under 35 U.S.C. § 102 (b) as being anticipated by Henrick *et al. Aust. J. Chem. 20*:2467-77 (1967) ("Henrick"). Compound XI of *Henrick* allegedly anticipates compounds of formula I when L is -C=O and both R_1 and R_2 represent alkylcarboxylate (Office Action, page 6). Applicants respectfully traverse this rejection.

Amended claims 47, 55 and 61 do not encompass compound XI of *Henrick* because both R_1 and R_2 of claimed compounds of formulae I-III do not represent alkylcarboxylate. Moreover, claims 48, 49, 52-54, 56, 59-60, 62 and 65 depend directly or ultimately from claim 47, 55 or 61. Thus, claims 47-49, 52-56, 59-62 and 65 are not anticipated by the teachings of *Henrick*. Accordingly, withdrawal of the rejection is respectfully requested.

Claims 47-49, 52-56, 59-62 and 65 are rejected under 35 U.S.C. § 102 (b) as being anticipated by Irwin, W. J., *et al.*, *J. Chem. Soc. Perkins I, 2*:250-252 (1974) ("Irwin"). Compound 7 of *Irwin* allegedly anticipates compounds of formula I when L is -C=O, R_1 represents alkyl and R_2 represents alkylcarboxylate (Office Action, page 6). Applicants respectfully traverse this rejection.

Amended claims 47, 55 and 61 do not encompass compound 7 of *Irwin* both because R_1 of claimed compounds of formulae I-III does not represent alkyl and because R_2 of compounds of formulae I-III is not alkylcarboxylate. Moreover, claims 48, 49, 52-54, 56, 59-60, 62 and 65 depend directly or ultimately from claim 47, 55 or 61. Thus, claims 47-49, 52-56, 59-62 and 65 are not anticipated by the teachings of *Irwin*. Accordingly, withdrawal of the rejection is respectfully requested.

Claims 47-49, 52-56, 59-62 and 65 are rejected under 35 U.S.C. § 102 (b) as being anticipated by Kuo, H.-S. *et al. J. Heterocycl. Chem. 16*:393-395 (1979) ("Kuo"). Compound V of *Kuo* allegedly anticipates compounds of formula I when L is -C=O, and R_1 and R_6 represent alkyl (Office Action, page 7). Applicants respectfully traverse this rejection.

Amended claims 47, 55 and 61 do not encompass compound V of *Kuo* because both R_1 and R_6 of compounds of formulae I-III do not represent alkyl. Moreover, claims 48, 49, 52-54, 56, 59-60, 62 and 65 depend directly or ultimately from claim 47, 55 or 61 and cannot encompass more than the independent claim from which they depend does. Thus, claims 47-49, 52-56, 59-62 and 65 are not anticipated by the teachings of *Kuo*. Accordingly, withdrawal of the rejection is respectfully requested.

Claims 47-49, 52-56, 59-62 and 65 are rejected under 35 U.S.C. § 102 (b) as being anticipated by Tewari, R. S. *et al. J. Chem. Eng. Data, 27*:101-103 (1982) ("Tewari '82"). Compounds 7a-7c and 9a-9g of *Tewari '82* allegedly anticipate compounds of formula I when L is -C=O, R_1 represents H or alkylcarboxylate and R_2 represents alkylcarboxylate (Office Action, page 7). Applicants respectfully traverse this rejection.

Regardless of the definition of L, R_1 and R_2, compounds of formulae I-III do not encompass compounds 9a-9g of *Tewari '82* because the position of the quinoline nitrogen in formulae I-III is different from the position of nitrogen in compounds 9a-9g. Therefore, compounds 9a-9g do not anticipate claims 47-49, 52-56, 59-62 and 65. Accordingly, withdrawal of this aspect of the rejection is respectfully requested.

Amended claims 47, 55 and 61 do not encompass compounds 7a-7c of *Tewari '82* because R_2 of compounds of formulae I-III does not represent alkylcarboxylate. Moreover, claims 48, 49, 52-54, 56, 57-60, 62 and 65 depend directly or ultimately from claim 47, 55 or 61 and cannot encompass more than the independent claim from which they depend does. Thus, claims 47-49, 52-56, 59-62 and 65 are not anticipated by the

teachings of *Tewari '82*. Accordingly, withdrawal of the rejection is respectfully requested.

Claims 47-49, 52-56, 59-62 and 65 are rejected under 35 U.S.C. § 102 (b) as being anticipated by Tewari, R. S. *et al. J. Chem. Eng. Data, 28*:283-285 (1983) ("Tewari '83"). Compounds 7a-7d and 9a-9h of *Tewari '83* allegedly anticipate compounds of formula I when L is -C=O and both R_1 and R_2 represent alkylcarboxylate (Office Action, page 7). Applicants respectfully traverse this rejection.

Regardless of the definition of L, R_1 and R_2, compounds of formulae I-III do not encompass compounds 9a-9h of *Tewari '83* because the position of the quinoline nitrogen in formulae I-III is different from the position of nitrogen in compounds 9a-9h. Therefore, compounds 9a-9h do not anticipate claims 47-49, 52-56, 59-62 and 65. Accordingly, withdrawal of this aspect of the rejection is respectfully requested.

Amended claims 47, 55 and 61 do not encompass compounds of formulae I-III wherein R_1 or R_2 is alkylcarboxylate. Moreover, claims 48, 49, 52-54, 56, 57-60, 62 and 65 depend directly or ultimately from claim 47, 55 or 61 and cannot encompass more the independent claim from which they depend does. Thus, claims 47-49, 52-56, 59-62 and 65 are not anticipated by the teachings of *Tewari '83*. Accordingly, withdrawal of the rejection is respectfully requested.

Claims 47-49, 52-56 and 59 are rejected under 35 U.S.C. § 102 (b) as being anticipated by Georgescu, E. I. *et al. Revue Roumaine de Chimie, 46*:357-362 (2001) ("Georgescu"). Compounds 8a-8d of *Georgescu* allegedly anticipate compounds of formula I when L is -C=O and Ar represents heteroaryl group (Office Action, page 8). Applicants respectfully traverse this rejection.

For *Goergescu* compounds 8a-8d to anticipate claims 47-49, 52-56 and 59, R_2 of compounds of formulae I-III must also represent alkylcarboxylate or acyl (see *Georgescu*, Table 2). However, R_2 of compounds of formulae I-III does not represent alkylcarboxylate or acyl. Therefore, claims 47-49, 52-56, 59-62 and 65 are not anticipated by the teachings of *Georgescu*. Accordingly, withdrawal of the rejection is respectfully requested.

The Examiner objects to claims 1-3, 5-8, 10, 11, 13-16, 18-22, 27-49, 51-56, 58-62, 64, 65 and 68 allegedly because they contain non-elected subject matter. Applicants respectfully traverse this objection.

Non-elected subject matter in claims 1-3, 5-8, 10, 11, 13-16, 18-22, 27-49, 52-56, 58-62, 64, 65 and 68 has been removed. Accordingly, withdrawal of this objection is respectfully requested.

Conclusion

All of the stated grounds of objection and rejection have been properly traversed, accommodated, or rendered moot. Applicants therefore respectfully request that the Examiner reconsider all presently outstanding objections and rejections and that they be withdrawn. Applicants believe that a full and complete reply has been made to the outstanding Office Action and, as such, the present application is in condition for allowance. If the Examiner believes, for any reason, that personal communication will expedite prosecution of this application, the Examiner is invited to telephone the undersigned at the number provided.

Prompt and favorable consideration of this Amendment and Reply is respectfully requested.

Respectfully submitted,

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